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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/717,845	11/19/2003	Ruth A, Gjerset	049146-1001	9478

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FOLEY & LARDNER LLP
P.O. BOX 80278
SAN DIEGO, CA 92138-0278

EXAMINER	
NGUYEN, QUANG	
ART UNIT	**PAPER NUMBER**
1633	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/717,845	GJERSET ET AL.	
	Examiner	Art Unit	
	Quang Nguyen, Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *22,24-29 and 31-39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22,24-29 and 31-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The application was transferred to Examiner Quang Nguyen, Ph.D. in GAU 1633.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/31/07 has been entered.

Claims 22, 24-29 and 31-39 are pending in the present application, and they are examined on the merits herein.

Claim Objections

Claim 35 is objected to because of the phrase "kidney or cells". I t appears that the term - - tumor - - is misspelled in the above phrase. Appropriate correction is required.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 22, 24-29 and 31-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Roth et al. (US 5,747,469) in view of any one of Lu et al. (Cancer Res. 62:1305-1310, 01 March 2002), Tango et al. (Hum. Gene Ther. 13:1372-1382, 20 July 2002) or DePinho, R.A. (US 6,613,750), and Teimann, F. (WO 01/11063) and Dirks et al. (US 6,060,273). ***This is a new ground of rejection.***

Roth et al described recombinant viral vectors such as retrovirus, adenovirus, AAV, HSV, or recombinant CMV vectors or recombinant non-viral vectors in liposomal formulations that express p53; and methods of treating cancers (e.g., benign and metastatic or malignant tumor cells including epithelial tumor cells, lung carcinoma and breast cancer cells) in a patient by administering the recombinant vectors to cancer cells in combination with chemotherapy or radiation therapy (see at least Summary of the Invention in cols. 3-9; and issued claims).

Roth et al did not teach specifically a method of inducing killing or apoptosis or growth arrest of malignant or metastatic p53-positive cancer cells by contacting said cells with a bicistronic contruct comprising a single promoter controlling the expression of a sequence encoding p53 and a sequence encoding p14ARF.

At the effective filing date of the present application (12/17/2002), Lu et al disclosed that tumors without a p53 mutation often resistant to p53 gene therapy (see at least the abstract). Lu et al. disclosed that a major factor in the resistance to p53 gene therapy involving p53+ tumor cells is likely to be loss of ARF expression in the p53+ tumor cells and the resultant inhibition and increased degradation of p53 mediated by MDM2 whose expression is induced by p53 but is inhibited by ARF (page 1307, col. 2 and page 1305, col. 1). Lu et al. showed that co-transfection with separate vectors encoding p14ARF and p53 was significantly more effective at inducing cell death in tumor cell lines (page 1306). Lu et al further taught that co-expression of p53 with p14ARF in gene therapy will be more effective for tumors that have p53+ tumor cells (page 1309, col.1).

Tango et al also disclosed that co-transfection of human cancer cells both *in vitro* and *in vivo* with recombinant vectors (administered simultaneously) expressing p14ARF (human homolog of the mouse p19ARF) and p53 greatly enhances the tumoricidal effect of either p53 or ARF gene therapy alone as ectopic expression of ARF enhances the effectiveness of p53 gene therapy (see at least the abstract). Tango et al. taught that p14ARF induces p53 upregulation by neutralizing the effects of MDM2, a transcriptional target of p53 that antagonizes its function.

DePinho already taught a method of inhibiting the growth of tumor cells based upon the discovery of p19ARF acts as a suppressor of oncogenic transformation by binding to the MDM2 oncoprotein and blocking MDM2's ability to target associated proteins such as p53 and Rb, for proteosomal degradation, said method comprises administering to tumor cells an effective amount of p19ARF and p53 in various forms, including in the form of an expression vector (see at least Summary of the Invention; particularly col. 8, lines 6-53; and issued claims). DePinho also taught that p19ARF includes human p19ARF or p14ARF which is human homolog of the mouse p19ARF (col. 7, lines 7-55; and issued claims). DePinho further disclosed thatp19ARF acts in a p53-dependent manner to inhibit cellular transformation (see at least col. 18, lines 50-54).

None of Lu et al., Tango et al., and DePinho taught specifically that both p53 and p14ARF nucleic acid sequences are present in a biscistronic construct and under the expression control of a single promoter.

Also at the effective filing date of the present application, Tiemann already described at least bicistronic viral vectors, e.g., retrovirus or AAV or non-viral vectors for the treatment of malignant or metastatic cancers, e.g., liver, breast, lung, melanoma or prostate, comprising coding sequence for p53 and p14ARF under control of a single promoter and separated by an IRES; and use of the same (e.g., as a pharmaceutical composition) in treating cancers (see the entire reference, especially, in the translation, at pages 8-12, and claims 1, 3, 17-19 and 22-28). Tiemann also disclosed that treating

tumor cells with both p53 and p14ARF genes resulted in synergistic killing of tumor cells (Figure 3).

Additionally, Dirks et al also taught the preparation and use of multicistronic expression units, including bicistronic units, containing a single transcriptional promoter (e.g., LTR, CMV, SV40), that allow the equimolar expression of the genes located in the corresponding cistrons (see at least the abstract and col. 5, line 22 continues to line 10 of col. 7). Dirks et al also noted the advantages of the disclosed multicistronic expression units over other alternatives including the use of multiple genes in separate expression vectors; multiple genes in independent transcription units on a vector or earlier versions of bicistronic or multicistronic vectors (see at least col. 1, line 21 continues to line 21 of col. 2).

It would have been obvious for an ordinary skilled artisan to modify the teachings of Roth et al. by also using a recombinant vector co-expressing p14ARF gene and p53 under the control of a single promoter in the form of bicistronic expression units taught by Dirks et al for treating benign and/or metastatic or malignant tumor cells, including p53-positive cancer cells, in a patient in light of the teachings of any one of Lu et al., Tango et al. or DePinho, R.A., together with Teimann.

An ordinary skilled artisan would have been motivated to carry out the above modifications because all of Lu et al., Tango et al. and DePinho taught that co-expression of p14ARF with p53 improved the effectiveness of p53 by blocking the inhibitory effects of MDM2 on p53. Moreover, Tienmann also taught that treating tumor

cells with both p53 and p14ARF genes resulted in synergistic killing of tumor cells; and that these two genes can be present in a bicistronic vector construct. Furthermore, the bicistronic expression construct of Dirks et al allows the equimolar expression of the genes located in the corresponding cistrons and it offered various advantages over alternative approaches including the use of multiple genes in separate expression vectors (problems associated with this approach include the ratio of the expression of the different genes to each other depends both on the copy number and on the site of integration in the genome of the host cell together with the assumption that several plasmids copies are simultaneously taken up in a stable manner and continue to be harboured following division), multiple genes in independent transcription units on a vector (This approach is based on the assumption that mRNAs encode different proteins possess the same stability and translation efficiency) or earlier versions of bicistronic or multicistronic vectors (the expression of the subsequent cistron is normally very low).

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of Roth et al. with any one of Lu et al., Tango et al. or DePinho, R.A., and with Teimann, F. and Dirks et al.; coupled with a high level of skill for an ordinary skilled artisan in the relevant art.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Response to Arguments

Applicant's arguments related in part with respect the above rejection in the Amendment filed on 10/31/07 (pages 5-6) along with the Declaration of Dr. Ruth Gjerset under 37 C.F.R. 1.132 filed on 10/31/07 have been fully considered but they are respectfully not found persuasive.

1. Applicants argue that the prior art provides no indication that a single promoter-bicistronic construct expression p53 and p14ARF would be significantly better than the use of individual vectors each expressing a single gene (dual-vector system) for killing p53-positive tumor cells since Kim et al (Exhibit B) cited Rucker et al., 1997 and noted that the longstanding recognition that the second gene of single promoter bicistronic vectors is underexpressed relative to the first.

Firstly, please refer to the teachings of Dirks et al. above. The bicistronic expression construct of Dirks et al allows **the equimolar expression of the genes located in the corresponding cistrons and it offered various advantages over alternative approaches** including the use of multiple genes in separate expression vectors (problems associated with this approach include the ratio of the expression of the different genes to each other depends both on the copy number and on the site of integration in the genome of the host cell together with the assumption that several plasmids copies are simultaneously taken up in a stable manner and continue to be harboured following division), multiple genes in independent transcription units on a vector (This approach is based on the assumption that mRNAs encode different proteins possess the same stability and translation efficiency) or earlier versions of

bicistronic or multicistronic vectors (the expression of the subsequent cistron is normally very low).

Secondly, it is also noted that arguments on whether or not a single promoter-bicistronic system is significantly better than the dual-vector system are irrelevant. This is because Tiemann already described explicitly the use of a single promoter bicistronic system for expressing both p53 and p14ARF for the treatment of malignant or metastatic cancers, e.g., liver, breast, lung, melanoma or prostate.

Thirdly, it would have been obvious for an ordinary skilled artisan to insert the p14ARF sequence immediately downstream of the promoter in a single promoter-biscistronic system and the p53 sequence immediately downstream of an IRES sequence for their co-expression in malignant or metastatic p53-positive cancer cells. This is because the expression of exogenous p14ARF in already p53-positive cancer cells is more critical due at least to its ability to induce p53 upregulation by neutralizing the effects of MDM2, a transcriptional target of p53 that antagonizes its function.

2. In the Declaration, Dr. Gjerset presented data comparing the relative effectiveness of the single promoter p53/p14ARF bicistronic vector with a dual vector system after taking into account of the possible differences in the level of infection of multiple vectors in the dual vector system by using moi from 10-200 for each vector. Dr. Gjerset showed that an moi of 10 for the single promoter bicistronic p53/p14ARF vector resulted in significantly more growth suppression than 200 moi of each of the p53 and p14ARF individual vectors used in combination, which represents approximately a 40-

fold increase in efficacy for the bicistronic vector. This effect is therefore surprising and unexpected in view of the relative comparability predicted by the prior art.

The examiner notes that calculations to arrive at the moi 10 that yields virtually 100% cells in the dual vector system to receive both vectors and the 40-fold increase in efficacy for the bicistronic vector are flawed because they did not take into account at least the following important factors such as: (1) the dominace of one vector over the other in copy number as well as expression in transfected cells; (b) cellular uptake of at least two different vectors in a stable manner; (c) mRNAs encoding p53 and p14ARF resulted from two different vector constructs may not possess the same stability and translation efficiency; (d) Cells already transfected with one vector may not have the same probability to be further transfected with another vector (same or different) as untransfected cells; all of which would obviously skewed the results in favor of the single promoter-bicistronic vector system.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (571) 272-0776.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's SPE, Joseph T. Woitach, Ph.D., may be reached at (571) 272-0739.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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QUANG NGUYEN, PH.D.
PRIMARY EXAMINER